CESREES

Comité Éthique et Scientifique pour les Recherches, les Études et les Évaluations en Santé

SIFNOS STUDY: RETROSPECTIVE STUDY IN PATIENTS WITH ATRIAL FIBRILLATION (AF) EXPOSED AND UNEXPOSED TO AN ORAL ANTICOAGULANT THERAPY BETWEEN 2016-2020 IN FRANCE

Version n°4.0

06 December 2021

Table of contents of the protocol

1. PRESENTATION OF THE PROJECT TEAM

Pfizer and BMS Project Team (Responsible for data processing – Non-English text , RT)

PPD , Pfizer, PPD

PPD , Pfizer, PPD

PPD , BMS, PPD

PPD , BMS, PPD

IQVIA Project Team (Responsible for the implementation of data processing – Non-English text , RMO)

PPD

PPD , IQVIA, PPD

This study is supervised by an expert committee comprised of:

Expert 1: Pr PPD , Dijon, Regional University Hospital

Expert 2 : PPD (Marseille, assistance publique-hôpitaux de Marseille (AP-HM)

Expert 3 : Pr PPD , Tours, Regional University Hospital

Expert 4 : Pr PPD , Paris, Broca Hospital, assistance publique-hôpitaux de Paris (APHP)

Expert 5: Pr PPD University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK

The scientific committee met on July 22, 2021 to define the objectives of the study, the different periods of the study and discuss on the proposed methodology. This protocol was validated by all the members of scientific committee of the study.

2. OBJECTIVES AND PURPOSES

2.1. Context, objectives and justification of the study

Atrial fibrillation (AF) is a heart rhythm disorder caused by abnormal electrical signals from the atria and is characterized by ineffective atrial contraction and irregular heartbeats. AF can occur in three forms: paroxysmal (episodes lasting less than 7 days), persistent or permanent (lasting more than 7 days) and irreversible (1).

Among patients with AF, more than one-third have associated valve disease, characterized by mitral stenosis or valve prosthesis (1). In this case, AF is called "valvular" (2). Conversely, in patients without associated valvular pathology, AF is said to be "non-valvular".

In France, two-thirds of AF patients are 75 years of age and older. The prevalence of AF is about 1% of the general population and increases with age to reach 10% of the population aged 80 years and over. The male/female sex ratio of prevalent cases is 3:2 (3). The absolute number of cases is equivalent between men and women because of the higher life expectancy in women (4).

Several pathophysiological mechanisms, including blood flow stasis, prothrombotic state, and hypercoagulability induced by AF, can lead to stroke (5). Clinical signs may include shortness of breath at rest, fatigue, palpitations, or chest pain. AF accounts for approximately 15% of all strokes (6).

The therapeutic management aims to prevent thromboembolic complications (risk multiplied by 5), in particular the occurrence of ischemic stroke, to reduce symptoms, to prevent recurrence of AF using antiarrhythmic treatment and to improve the quality of life of patients (4). The 2014 Guidelines of the French National Authority for Health recommend initiating an oral anticoagulant (OAC)in AF patients to prevent the risk of stroke in the event of a high thromboembolic risk identified by a CHA2DS2-VASC score greater than or equal to 2. If the score is equal to 1, the initiation is to be discussed according to risk factors. Among the OACs, the antivitamins K (VKA) (warfarin, acenocoumarol - and fluindione until 2017) were considered as the reference drugs until 2017; the direct oral anticoagulant (DOAC) including direct factor Xa inhibitors (rivaroxaban and apixaban) and direct thrombin inhibitor (dabigatran) could be prescribed as an alternative (4). Recommendations concerning the good use of OACs has been updated in 2018 (5)**. Since then, DOAC can also be prescribed as a first-line treatment** in non-valvular AF patients.

The main risk associated with the use of OACs is the occurrence of serious bleeding events requiring careful use and regular treatment reevaluation. Among patients with AF, some populations have this risk of bleeding potentially increased, especially the elderly and frail (8,9), or those having dementia (10). The risk is also increased in patients with coronary arterial disease (CAD) due to antithrombotic therapy with dual antiplatelet and OAC (4). In case of contraindication to oral anticoagulation, in particular because of major risk of bleeding, a left atrial appendage (LAA) occlusion may be considered to prevent the risk of thromboembolism (11,12)

In France, two previous studies published by Santé Publique France described the annual rate of adult patients newly treated with OAC for AF using data from the National Health Data System (SNDS), of which the most recent published in 2021 estimates in 2018 a standardized rate of 410/100,000 inhabitants (6,7). To our knowledge, no such recent French epidemiological data specific to AF unexposed to OAC is available.

The use of OACs and the associated risks were evaluated in the NACORA study conducted in 2014 by the National Health Insurance (CNAM) in collaboration with the National Agency for Medicines and Health Products Safety (ANSM), using data from the SNDS. This study assessed in France, the hemorrhagic and thromboembolic risks in AF patients exposed to VKA and DOAC (rivaroxaban and dabigatran only), over a short exposure periods of 6 months and a study period from 2011 to 2012 (13,14).

Pfizer and BMS laboratories conducted the NAXOS study, following the methodology of the NACORA study, published in 2020, for the reassessment of the reimbursement of apixaban on the data from the SNDS. The NAXOS study compared the 1-year risk of occurrence of stroke and systemic embolism (SE) and major bleeding in patients initiating OACs (apixaban, rivaroxaban, dabigatran, and VKAs) between 2014 and 2016 with AF (15).

By contrast, there is no such data in AF patients unexposed to OAC in France. This study aims to address the lack

of safety data in the population of AF patients unexposed to OAC over a recent period: 2016-2020. It will also serve as an opportunity to update data in the population of exposed patients since no new results have been published since 2016 and to focus on subpopulations most at risk. Furthermore, the study will allow to describe the changes in AF management following the recommendations issued by the HAS in 2018 .

The objectives of the SIFNOS study are:

Primary objective

To estimate the incidence rate of stroke (ischemic or hemorrhagic), major bleeding and death in both non-valvular AF patients exposed to OAC (VKA or DOAC) and unexposed to OAC, overall and in the following subgroups of interest:

- Elderly (≥80 years old)
- Patients with CAD
- Frail patients
- Patients reported with active cancer
- Patients reported with previous stroke

Secondary objectives

- To describe the characteristics of non-valvular AF patients exposed and unexposed to OAC
- To compare the incidence rate of stroke, major bleeding, and death between those two populations
- To estimate the annual incidence and prevalence of patients with non-valvular atrial fibrillation (AF), exposed and unexposed to OAC
- To describe the use of oral anticoagulants (OACs) in non-valvular AF patients initiating treatment (AF patients exposed to OAC therapy)
- To compare Healthcare Resource Utilization (HCRU) and associated costs between patients exposed to apixaban, rivaroxaban, dabigatran, VKA and patients unexposed to OACs
- To describe the therapeutic management before/after the first stroke occurring after initiation of OAC exposure

Exploratory objectives

- To identify subgroups among AF patients with similar profile

2.2. Respect of ethics

This study does not involve the collection, use or transmittal of individually identifiable patient / subject data. It will be conducted in accordance with the ethical and French legal framework, the main principles of which: respect for people, beneficence, non-maleficence and justice. It will process only reimbursed pseudonymized data from SNDS.

2.3. Justification of the public interest

Pfizer and BMS need for scientific research purposes, to use the National Health Data System (SNDS) databases in order to have more recent data and to consider any changes in the management of AF patients during the 2016-2020 period and wish to update the NAXOS study (finalized in 2016 and submitted to the authorities in 2020). Unlike the previous NAXOS study, the SIFNOS study will extend the epidemiological data to all patients having non valvular AF (exposed or unexposed to OAC). It will provide data of AF patients, on their socio-demographic characteristics, care pathways and healthcare resource utilization and incidence rate of clinical outcomes. The incidence rate of clinical outcomes, stroke, major bleeding, and mortality will also be studied in AF subpopulations of interest. This knowledge is intended to provide additional data to optimize the management of patients in routine practice.

2.4. Publication and communication of the results

The results of this study could be communicated trough a scientific publication in a scientific peer reviewed journal. The publication will be written in collaboration with IQVIA and Pfizer/BMS. Posters or oral presentations will be prepared for relevant scientific events. The results will be presented as supportive evidence in regulatory submissions to French health authorities, if necessary.

3. METHODOLOGY

3.1. Study design

3.1.1. Description of the study design

SINFOS study is an observational retrospective cohort study using French national health insurance claims database (SNDS). A unique extraction of AF patients (exposed or unexposed to OAC therapy) in SNDS data will be used to conduct the study from 2016 to 2020.

The outcomes are assessed by study objective and defined in Appendix 2, Table 1.

3.1.2. Study time periods

Periods and dates of the study

Inclusion period: Patients will be included from January 1st, 2016 to December 31st, 2019 and to December 31st, 2020 in sensitivity analyses.
Note: Given the uncertainty of the impact of the Covid 19 health crisis on the management of AF patients, for all analyses, the 2020 data will be excluded but included in sensitivity analyses.

Index date for the AF population: The index date will correspond to the date of the first diagnosis of AF, identified by the date of the start of LTD or of the index hospital stay (patients newly diagnosed AF during the study period) and if not filled in (i.e. identified by the initiation of an OAC) to the date of initiation of the OAC for OAC new users.

Historical period: A lookback period of 2 years will be considered before the index date in order to distinguish incident and prevalent AF-patients, describe patient's comorbidities, medical history and history of treatments. Consequently, this historical period will start from January 1st, 2014.

Follow-up period Follow-up will start on the index date and end on the date of occurrence of one of the following events: death or the end date of the study (December 31th, 2019 and to December 31st, 2020 in sensitivity analyses, or the date of the last reimbursement of care recorded in the SNDS (patients with no consumption or reimbursement of care in the 12 months following the date of last consumption).

Data extraction period: The data extraction period will start on January 1st, 2014 and end on December 31st, 2020.

3.2. Description and justification of the study population

3.2.1. Study population

This retrospective cohort study focuses on the AF population as described in

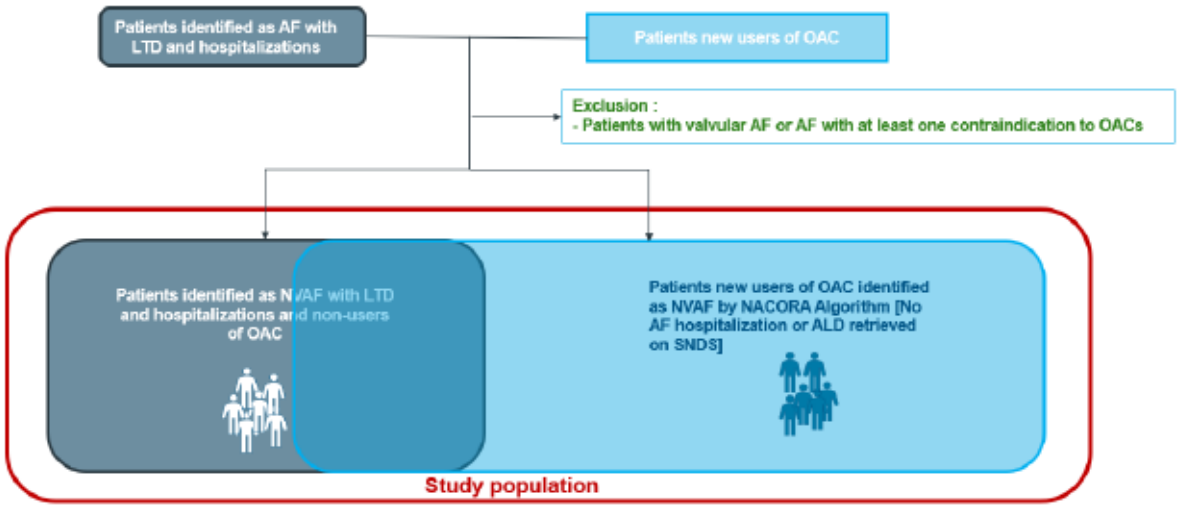

Figure 1, in Appendix 2.

The inclusion criteria for the AF population are:

- Patients with at least one hospital stay with a principal (PD), related (RD) or associated (AD) diagnosis of code I48 (Atrial fibrillation of the International Classification of Disease 10th version, ICD-10) or with an active Long-Term Disease (LTD) at the index date or during the year with ICD-10 code I48;

OR

- Patients who are new users of OACs for the AF treatment with or without AF diagnosis (PMSI-MSO or LTD), identifying with a validated and published algorithm with a high specificity (c-index 0,93), using a predictive model developed in the NACORA study (14,16). The algorithm for identifying patients exposed to OAC indicated for AF is based on the presence of at least one reimbursement of an OAC (VKA, apixaban, rivaroxaban or dabigatran), without use of the same OAC in the 24 months prior to the first reimbursement date. This algorithm considers reimbursement data for the 6 weeks prior to the first OAC reimbursement to distinguish patients treated for AF from those treated for deep venous thrombosis (DVT) or pulmonary embolism (PE). This algorithm includes data on age, gender, use of treatments as use of beta-blockers, antiarrhythmics, antiplatelets, antihypertensive drug, holter/echocardiography procedures, cardiologist prescriber, D-dimer blood test reimbursement.

The exclusion criteria for the AF population correspond to those applied in the NACORA and NAXOS studies and are:

- Patients with at least one hospital stays with an ICD-10 code in PD, RD or AD for associated valve disease, ICD-10 codes I05 to I09, I34 and I39, or valve surgery;
- Patients treated with an OAC for another indication than AF:
  - Patients who are new users of OACs for the treatment of pulmonary embolism (PE, ICD-10 code I26), or deep vein thrombosis (DVT, ICD codes I80 to I82);
  - Patients who are new users of OAC, not indicated for AF, PE and DVT, having in the six weeks preceding the first reimbursement of OAC, an orthopedic procedure (osteoarticular or muscular) of the lower limb (including hip/knee replacement) as corresponding to the indication of primary prevention of venous thromboembolic events (root of the Diagnosis Related Group , DRG D02)

The following table summarizes the criteria for selecting patients from the AF population in the SNDS data.

Cohort	Inclusion criteria	Exclusion criteria
AF Population	o Identified patients with AF aged 18 years and older at diagnosis of AF	o - Beneficiaries who are insufficiently identifiable or for whom there are technical

		constraints in SNDS [fictive pseudoNIR (patient identifier), twins]; o - Beneficiaries affiliated to a settlement institution from the oversea French department Mayotte; o History of valvular pathology and contraindications to OAC treatment.

Note: Other exclusion criteria will be discussed together with the Scientific Committee

3.2.2. Subpopulations

To meet the objectives of the SIFNOS study, different subpopulations will be split in:

- Elderly AF patients stratified on age-group (≥ 80 years old)
- AF patients having a history of coronary arterial disease (CAD),
- AF frail patients
- AF patients having an active cancer
- AF patients reported with previous stroke.

3.3. Study size

All analyses (except the estimation of the prevalence of AF) will be conducted in patients newly diagnosed with FA. In 2018, a study conducted by Santé Publique France, showed that 225,747 AF patients were OAC new users (6). If the number of new patients remains constant during the study period of 5 years from 2016 to 2020, we expect that approximately 1 million patients will be exposed to OAC in the SIFNOS study.

3.4. Data sources

The study will be conducted using data from the following SNDS databases:

- Outpatient claims database (DCIR - *Données de Consommation Inter-Régime*): Main healthcare claims database, which covers 98.8% of the French population.
- Hospital discharge summaries database (PMSI - *Programme de médicalisation des systèmes d'information*): National hospital discharge database, including public and private hospitals.

Details on information contained in each database is presented in Appendix 1 .

3.5. Variables

3.5.1. Covariates

An indicative list of parameters available in the proposed data sources are shown in Table A1. 5.

3.5.2. Exposure

Exposure to an OAC is defined by an initiation of VKA, apixaban, dabigatran or rivaroxaban.

AF patients unexposed to OAC are defined by a first diagnosis of AF without OAC treatment.

3.5.3. Stratification

All analyses on AF patients will be stratified on age-group: <80, 80-90, > 90 years old.

All analyses on AF patients exposed and unexposed to OAC, will be stratified on **modified CHA_2DS_2VASC score strata** (18), low risk (score 0 in males or 1 in females); moderate risk (score 1 in males or 2 in females); high risk if ≥2 for males and ≥3 females.

All analyses where the event of interest is stroke, will be stratified on ischemic or hemorrhagic stroke.

3.6. Data management

Data management for this study will be conducted using standard IQVIA processes. Further details on the data handling procedures will be provided to Pfizer and BMS in the statistical analysis plan (SAP) and/or in the Data Handling Plan. The process would take into consideration any data governance imposed on the data source including any plans to handle the data outside of the institution or country of origin. IQVIA will adhere to all local and regional laws on data protection and privacy.

The internal code of good practices grouping all IQVIA commitments related to accessibility, circulation, protection and handling of personal health data will be implement. In the context of this project, this code relates to the use of SNDS data through accessing the National Health Insurance database portal.

IQVIA will develop the queries, the management and the statistical analysis of the exploited data using SAS® Entreprise Guide version 7.1.

Given the exhaustive nature of the SNDS data and the very high completeness rate of the variables in its databases, it does not seem justified to use methods of imputation of missing data.

3.7. Data treatment and analyses

<u>General considerations on statistical analyses</u>

Categorical or discrete variables will be described with counts and percentage observed on each modality. Quantitative variables will be described with standard statistics including numbers (available, missing), mean, standard deviation, median and quartile of order 1 and 3, minimum and maximum.

3.7.1 Outcomes of primary objectives

Estimation of incidence rate of stroke, major bleeding, and death in both non-valvular AF patients exposed to OAC (VKA or DOAC) and unexposed to OAC, overall and in the subgroups of interest.

In **longitudinal analyses**, for each AF populations and subpopulations of interest defined in section 3.2.2, the annual cumulative incidence will be estimated from the occurrence of each of the events of interest, stroke, major bleeding, and death, during patient follow-up. The annual cumulative incidence will be defined as the number of events occurring during the follow-up period divided by the number of person-years of follow-up.

3.7.2 Outcomes of secondary objectives

3.7.2.1 To describe the characteristics of non-valvular AF patients exposed and unexposed to OAC and to compare the incidence rate of stroke, major bleeding, and death between those two populations

In **cross-sectional analyses and every year**, we will describe for AF subpopulations, sociodemographic characteristics, comorbidities, medical history of interest and associated treatments defined in Table A1.

The modified $CHAD_2DS_2VASC$ score for thromboembolic risk and HAS-BLED (19) for hemorrhagic risk will be estimated every year during the study period using adapted algorithms to SNDS.

3.7.2.2 Comparison of the incidence of stroke, major bleeding, death

To compare the incidence of clinical outcomes, stroke, major bleeding and death, in AF patients exposed and unexposed to OAC therapy, **in longitudinal analysis**, we will use a comparison of cumulative incidence rate using a Cox regression model **with OAC exposure considered as time-dependent variable** adjusted for covariates (or IPTW if necessary) (Figure 2, Appendix 2). This analysis will be performed twice, firstly by comparing patients exposed to dabigatran, apixaban, rivaroxaban *vs.* patients exposed to VKAs and secondly for AF patients with a high thromboembolic risk (if modified CHA_2DS_2VASC score is ≥2 for males and ≥3 females) by comparing patients exposed to DOACs combined in one class vs VKAs *vs.* unexposed patients for patients. By applying the OAC exposure variable as a time dependent variable, estimates of Hazard Ratio will account for switches and discontinuations. In this analysis, the reference will be VKA exposure. **Censor is defined as** patient's last health record or date of end of follow-up.

3.7.2.3 Estimation of the annual standardized incidence rate and prevalence

In cross sectional analyses per calendar year to 2016 to 2019, annual standardized incidence rate and annual prevalence, defined in Table A1. 1, will be estimated (N per 100,000 inhabitants).

3.7.2.3 Description of OAC treatment patterns

In longitudinal analysis during the study period, in AF patients exposed to VKA, apixaban, rivaroxaban, and dabigatran, we will describe the OAC treatment patterns, using a treatment sequence analysis, to define lines of treatment (LOT), switches of OAC, concomitant treatments and temporary or permanent discontinuation. We will use an adaptation of Sankey diagrams for the visualization. We will define the dominant therapeutic management and characterize prescription fills. Patients must have received at least one delivery of apixaban, dabigatran, rivaroxaban, VKA within the entire follow-up to be included in the treatment pattern analyses. Other information such as prescriber's characteristics at each coverage period (hospital or private medical practice and prescriber's specialty) and the type of AF treatment(s) used will be considered.

The treatment pattern analysis will provide the following information:

- Number and percentage of patients receiving each of OAC treatment
- Percentage of patients who received 1, 2, 3, 4 and 5+ LOTs during the follow-up
- Analyses of duration of treatment by LOT
- Time to next treatment (TTNT) changed by line of treatment

Persistence rate to OAC at 6 and 12 months after the initiation will be estimate by Kaplan-Meier curves

3.7.2.4 Description of the therapeutic management before/after the first stroke occurring after initiation of OAC therapy

To describe the therapeutic management before/ after the first stroke in AF patients exposed to dabigatran,

apixaban, rivaroxaban, VKA and unexposed to OAC i.e. 5 classes, in **cross-sectional analysis at 6 and 12 months before and after the first stroke**, we will describe HCRU (ambulatory care, hospital care, rehabilitation care facilities and medications) defined in Table A1. 2.

3.7.2.5 Comparison of HCRU and associated costs

In **cross-sectional analyses every year of follow up,** HCRU and associated costs including event-related costs (i.e. stroke related and/or bleed related) defined in Table A1. 3, will be compared between AF patients exposed to apixaban, rivaroxaban, dabigatran, VKA and unexposed to OAC from index date to end of follow-up, including number and rate of patients using each resource by year of follow up, and the rate per patient per month (PPPM). All costs will be provided in Euros, annualized based on 2019 prices and presented PPPM. Cost analysis will be performed from the health insurance perspective (reimbursed costs). Costs and resource use will be presented PPPM, to consider differences in follow-up duration. Mean of costs of HCRU defined in Table A1. 4, will be compared between AF patients exposed to apixaban, rivaroxaban, dabigatran and exposed to OAC vs AF patients exposed to VKA.

For the comparison of average of costs, significant differences between groups will be detected by means of the Student test for equality of means. Prior to this, the Fischer test will have enabled us to verify the hypothesis of equality of variances and the Shapiro Wilk test the hypothesis of normality. In the event of non-verification, a non-parametric approach will be preferred; the Wilcoxon or Mann-Whitney test for comparisons between 2 groups and the Kruskal-Wallis test beyond 2 groups will be considered. The tests will be two-sided with a significance level of 5%.

3.7.3 Outcomes of exploratory objectives

3.7.3.3 Identification of subgroups among patients with similar profile with clustering models

To identify subgroup of AF patients with similar profile, we will use clustering models (K-Means, Random-Forest, Ascending hierarchical clustering) with a data visualization.

3.7.4 Stratified analyses

Secondary objectives analyses will be stratified on:

- Patients having a malnutrition,
- Patients at risk of falls identified by an algorithm adapted to SNDS data,
- Frail patients identified by Claims based Frailty Index (CFI) adapted to SNDS data,
- AF Patients with one or more comorbidities identified by age-adjusted Charlson comorbidity index (ACCI) adapted to SNDS data,
- Patients having a morbid obesity,
- Patients with a history of ischemic or hemorrhagic stroke,
- Patients with a history of major bleeding,
- Patient with at least one visit to a nursing home
- Patients with a history of dementia

3.7.5 Sensitivity analyses

We will perform following sensitivity analyses:

- **All analyses** will be conducted including the 2020 data, given the uncertainty of the impact of the Covid 19 health crisis on the management of AF patients
- AF patients without the second inclusion criteria, OAC new users identified by algorithm used in NACORA study to estimate the standardized incidence rate and prevalence.

3.8 Limits of the study

Limitations of this study include those inherent to the use of retrospective administrative claims data and limitations associated with missing data. Several limits related to the use of SNDS data have been identified in this study, no biological and clinical information were available for this study. The drug intake of patients is not measurable. Health insurance scheme: the dates of death and information on long term disease (LTD) for the self-employed and agricultural schemes (MSA/RSI) as well as for SLMs (government employees and student schemes) are partially available in the DCIR.

3.9 Milestone and project feasibility

Milestone	Planned dates
Scientific committee meeting	July 2021
Review of protocol by SC members	July-August 2021
Regulatory submission of the project to HDH	September 22, 2021
CESREES opinion about the project	December 2021
CNIL approval	February 2021
Review of study statistical analysis plan by SC members	March 2022
CNAM – IQVIA- Pfizer/BMS agreement Signature S	September 2022
Data access by CNAM	October 2022
Data management and analysis by IQVIA	October 2022 - January 2023
Validation of the results and study report redaction	February 2023
Study report delivery and Review of the report by SC members	March 2023

IQVIA has experience and capabilities:

- Strong knowledge of the French healthcare system
- A multi-disciplinary team with complementary skills: Capabilities in epidemiology, statistics and machine learning in the same team
- Experience in performing retrospective studies using public data (cohorts, SNDS)

4 PRIVACY PROTECTION, DATA SECURITY AND CONFIDENTIALITY

(Section destinée à la CNIL)

The treatment of health personal data (including SNDS database), in order to respects patients' liberties and rights, are subject to the provisions of the French IT and liberties law (*Loi Informatique et libertés-LIL*), the French Public health code and the European General Data Protection Regulation (GDPR). The Study will be conducted on the legal basis of and in compliance with article 9.2 (j) of the GDPR.

4.1 Information of patients and right protection

4.1.1 Individual information of the patients

This study is conducted on SNDS databases, patient information is the CNAM responsibility as the data controller. Therefore

Individual information is not required for studies conducted in the unique SNDS database, we request a waiver of the individual information. Individuals are informed about SNDS existence and of the possible re-use of their data for research purposes on different websites (hospitals, health insurance companies etc.), posters or even delivered documents.

4.1.2 Respect of human rights

This respect of individual rights for this study conducted in SNDS databases is the CNAM responsibility as the data controller.

The procedures and measures taken to respect the patients' rights include as follows:

- The non-reidentification of the patients: SNDS databases only contain pseudonymized data. The pseudonymization process was built to be non-reversible.
- The limitation of data storage duration: CNAM will archive and store the project file including data extracted from the analyses and the results' tables, for a period of 3 years after the publication of the results, according to the request sent to the French data protection authority (CNIL).
- The implementation of a process allowing patients' to fully exercise their rights: this notably concerns possibility of being informed about the ongoing studies, the data reuse, their right to access and to object. The ongoing studies and the possible reuse of data are mentioned on the Health Data Hub webpage (the SNDS is part of the Health Data Hub). The right of access, the right of rectification and the right to object are exercised, under the conditions defined in Articles 92 to 95 (modified decree n°2005-1309 of 20 October, 2005), to the managing body director of the compulsory health insurance scheme to which the patient is affiliated.
- The confidentiality of the data: in accordance with the provisions relating to the confidentiality of information concerning, in particular, the studies, the persons involved, and the results obtained (Article R. 5121-13 of the Public Health Code), persons with access to the data will take all necessary precautions to ensure the confidentiality of the information they contain. These persons are subject to professional secrecy (according to the conditions defined by articles 226-13 and 226-14 of the penal code).

4.2 Data support and security

4.2.1 Managing the risk of re-identification

Compliance with RGPD standards for aggregated data tables.

4.2.2 Data support

Implementation of Standard Operating Procedure (SOP), as well as specific SNDS Work Instruction (SNDS_FRWI_001) grouping all IQVIA commitments related to accessibility, circulation, protection and handling of personal health data.

In the context of this project, this internal code of good practices relates to the access and use of SNDS data exclusively through the National Health Insurance fund portal (CNAM portal) and the strict respect of this portal access rules imposed by the CNAM and the CNIL.

1. Protected access to SNDS within the scope of the study

Access to SNDS will be limited only to the people designated by the responsible for the project and who have undertaken the training necessary for the use of DCIR data after receiving a prior authorization from the Data Protection Authority (CNIL). The requests for qualification will be limited to 5 people for the present project. Each person will sign the document related to the general conditions for use of health data sent by CNAM upon request for access to the SNDS portal, such access will include the SNDS data herein. The period of access to SNDS will cover only the time necessary for the good performance of the project and will not exceed the period specified in the CNIL agreement.

2. Handling / Search of individual data

Handling and/or search applied to the individual data will be strictly done within the CNAM portal, in the study-dedicated project space. Likewise, all tables of individual data required for the analyses will be stored in this space. At the end of the study, the dedicated project dossier will be transferred into the CNAM archiving system. Thus, no individual data will be exported from the CNAM server.

3. Highly secured access to the portal

Qualified users have to connect to the portal respecting a two-step highly secured process, with personal instant pass-word connection edition.

4. Access to traceability after connections

Once connected, all connections and actions of qualified people made in the SNDS portal within the scope of the study may be tracked by the CNAM for conformity controls.

5. Data storage duration

CNAM will archive and store the project dossier including data extracted from the analyses and the results' tables, stored for a period of 3 years after the publication of the results, according to the request sent to CNIL.

6. Non-reuse of data

IQVIA undertook not to reuse the individual data handled in the SNDS portal within the scope of this study and out of the present project.

4.2.3 Data circulation and matching

Only data from SNDS database will be used, without any matching to another database. Extracted data are available in a dedicated project space on the CNAM secure web portal. The data provision is ensured by the DEMEX team, belonging to the CNAM *Direction de la Stratégie, des études et des statistiques (DSES)*.

IQVIA has developed an internal code of good practices including all the commitments regarding access, circulation of personal health data. Regarding the present study, this code refers to the use of SNDS data through the CNAM secure web portal. This point relative to data security is detailed in section 4.2.

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6 SUPPLEMENTARY MATERIAL

Appendix 1 SNDS databases presentation and contents

Presentation of SNDS databases

The French health insurance information system (Système national d'information interrégimes de l'Assurance Maladie, SNIIRAM) was created in 1999 to track health care consumption and expenditures. It has been improved over time in terms of exhaustiveness and information availability. SNIIRAM has continued to grow and extend to become, in 2016, the cornerstone of the national health data system (Système National des Données de Santé, SNDS).

The SNDS now covers 98.8% of the French population, over 66 million persons, from birth or immigration to death or emigration. It contains individual data used for billing and reimbursement of outpatient health care consumption (DCIR database – inter-scheme consumption data) collected by the health insurance, private and public hospital data (PMSI database) and causes of death (National death registry, CépiDC) for some years. It will also gradually integrate social and medical data and data from complementary health insurance. Outpatient and hospital care data are collected from the social security card, treatment forms, private institution invoices and procedures and outpatient visits billed by hospitals.

DCIR database

Sociodemographic characteristics

Patient's gender, date of birth, eligibility for complementary universal healthcare insurance (CMUc), localization of residence, date of death (month and year), indicator of low income.

Reimbursed/medical data

- Long Term Disease (LTD) registration with start and end dates (costly chronic diseases, with ICD-10 codes). It is requested by the patient's practitioner and medically validated by the health insurance system. Once registered, patients receive full reimbursement for expenditures related to the LTD.
- Dates of professional healthcare visits (general practitioners, specialists, paramedics) and mode of exercise (private of public practice);
- Date and nature of realized lab tests (coded with the nomenclature code of the medical biology acts [NABM]), medical procedures (coded with CCAM) without medical indication nor results, dates of prescription and completion, total and reimbursed costs;
- Drugs prescribed and reimbursed (pharmacy deliveries), medical devices, with prescriber and professional caregiver information (specialty, private/public practice). Nature of drugs (Anatomical Therapeutic Chemical [ATC] codes), nature of medical device (List of Products and Services [LPP]), number of units, date of prescription, total and reimbursed costs are also available for the drugs/medical device dispensed;
- Information on occupational diseases and sick leaves;

PMSI database

This national hospital discharge database is handled by the Agency for information on hospital care (ATIH); it contains exhaustive hospital health care consumption: hospitalizations in short-stay institutions (medicine, surgery, obstetrics and odontology: French acronym MCO), in aftercare and rehabilitation (SSR), in psychiatry (RIM-P) and hospital at home (HAD).

PMSI-MCO includes:

- Patients' demographics: date of birth, gender;
- Hospital national entity identifier;
- ICD-10 codes for primary diagnosis, associated diagnosis, and linked diagnosis for ICD-10 Z-codes (e.g. chemotherapy sessions), for all private and public medical, obstetric and surgery hospitalizations;
- Entry and discharge dates (only month before 2010, full date since), duration of hospitalization;
- Date and nature of medical procedures performed including surgery or imaging (conventional imaging, scans, resonance imaging [MRI], etc) coded according to the French common classification of medical procedures (CCAM); no indication nor results of these exams are provided though;

- Cost coding system (Diagnostic Related Group);
- Nature of on-top-of-DRG drugs (costly innovative and listed drugs on the "Non-English text") dispensed and administered during hospital stays (coded according to the inter-pharmaceutical code [CIP] and/or the anatomic therapeutic and chemical classification [ATC]), date of administration;
- Nature of implantable medical devices implanted during hospital stays, coded according to the LPP;

The hospital discharge summary also includes the medical unit summaries. PMSI data are available yearly in the SNDS, during the third trimester of current year for the data of previous year.

List of covariables of interest

ICD-10, CCAM and ATC codes to identify OAC exposure, clinical events of interest, associated treatments, LAA occlusion, comorbidities of interest and medical history are presented in Appendices 3,4 and 5.

Table A1. 5 : Indicative study parameters

Parameter	Description/Definition
Sociodemographic characteristics	Age, sex, complimentary universal health care (CMU-c), aid for complementary health care (ACS) for elderly patients, department of patient's residence
Medical history and comorbidities	Identified algorithmically with hospital diagnoses, active long-term disease, drugs and medical procedures: Coronary arterial diseases (CAD), Dementia (Alzheimer dementia/vascular dementia/other dementia), Ischemic or hemorrhagic stroke (intracranial bleeding) Congestive Heart failure, Peripheral arterial disease, Other vascular diseases; Sleep disorders; Active cancer (within 6 months in the historical period) Age adjusted Charlson Cormordity Index (ACCI) adapted to the SNDS data (20) ; Frail patient identified by Claims-Based Fragility Index (CFI) adapted to the SNDS data (21) ; Malnutrition ; Morbid Obesity; Anemia; COPD Diabetes Patients at risk of falls identified by an algorithm adapted to SNDS data (22) ; Patients poly-medicated Patient with at least one nursing home entry available
Drug exposure	AF patients exposed to VKA, apixaban, rivaroxaban, dabigatran AF patients unexposed to OAC
Associated treatments	Beta-blockers, antihypertensives, antiplatelet drugs, other anticoagulants, Non-steroidal anti-inflammatory drugs (NSAIDs), oral corticoids, proton pump inhibitors, Selective serotonin reuptake inhibitor antidepressants (SSRIs), systemic azole antifungals, medical procedure of cardioversion, CYP P450 inhibitors, protease inhibitors
Left atrial appendage (LAA) occlusion	Medical procedure of treatment of thromboembolic risk in AF in alternative of OAC
Modified risk scores in AF	Thromboembolic risk: **Modified CHA_2DS_2VASC** identified by an algorithm adapted to SNDS data Hemorrhagic risk: **Modified HAS-BLED** identified by an algorithm adapted to SNDS data

Parameter	Description/Definition
Annual standardized incidence rate of AF	Ratio of number of newly diagnosed non valvular AF patients to the number of individuals in the French population per calendar year (N per 100,000 inhabitants) standardized on age using the 2019 French population structure and 2020 in sensitivity analyses.
Annual prevalence of AF	Ratio of number of diagnosed NVAF patients to the number of individuals in the French population (INSEE data) per calendar year (N per 100,000 inhabitants).
OAC treatment patterns **Line of treatment / regimen**	Identified algorithmically using drug regimen, duration of treatment, and gaps between treatments. Number of lines of treatment (LOT), duration of treatment, time to next treatment will be estimated
Hospitalizations and length of hospitalizations per LOT	Identified with hospital diagnoses (primary, related, associated) and with the date of admission and date of exit from this hospitalization.
Clinical events of interest	Stroke (ischemic/ hemorrhagic) Major bleeding Death
Healthcare Resource use (HCRU) and costs	**Ambulatory care** Medical consultations and outpatient visits Medical and technical procedures, imaging, biologic tests Healthcare providers visits **Hospital care (MCO)** Hospitalizations, emergency room admissions Medical and technical procedures, imaging… **Rehabilitation care facilities (SSR)** **Medications** Including: Anticoagulants, antiplatelets, antihypertensive drugs glucose-lowering drugs, lipid-lowering drugs, antiarrhythmics, beta-blockers
Costs of HCRU	Health insurance perspective of direct costs of HCRU per resource used (ambulatory, hospital care, rehabilitation care…)

Appendix 2 List of figures and tables

Outcomes	Primary objective	Secondary objective	Exploratory objective
Incidence rate of stroke, major bleeding and death in AF patients (exposed/unexposed), overall and in subgroups	✓		
Annual standardized incidence rate and annual prevalence		✓	
Characteristics of AF patients and associated treatments		✓	
OAC treatment patterns		✓	
Comparison of the incidence rate of stroke, major bleeding, death		✓	
Therapeutic management before/after the first stroke occurring after initiation of OAC therapy		✓	
Impact of an OAC switch on the onset of stroke or death		✓	
Comparison of HCRU and associated costs		✓	
Identification of subgroups among patients with similar profile by clustering models			✓

Table 1 Outcomes by study objective

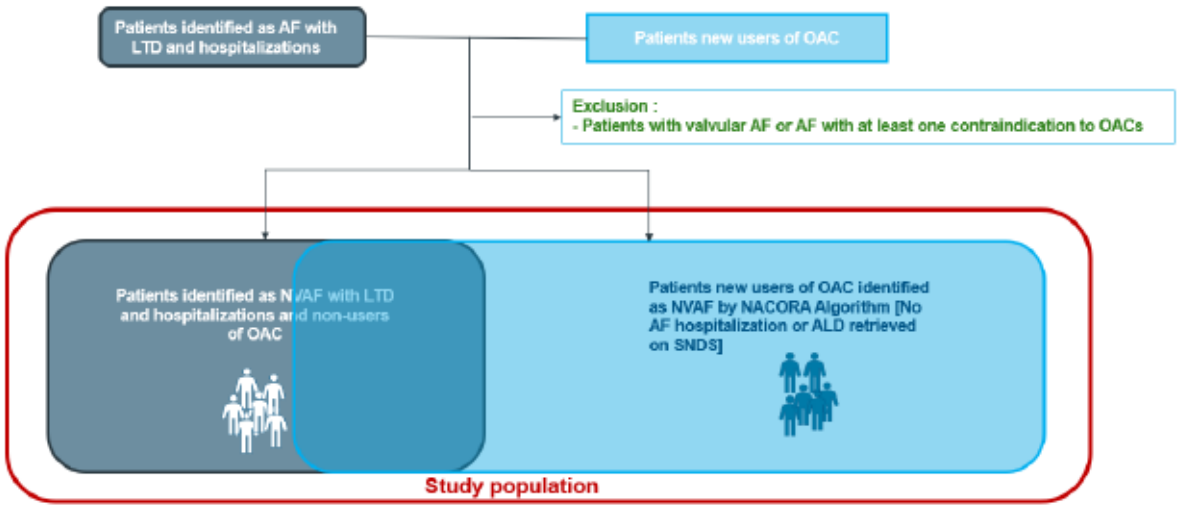


Figure 1. AF study population according to inclusion and non-inclusion criteria

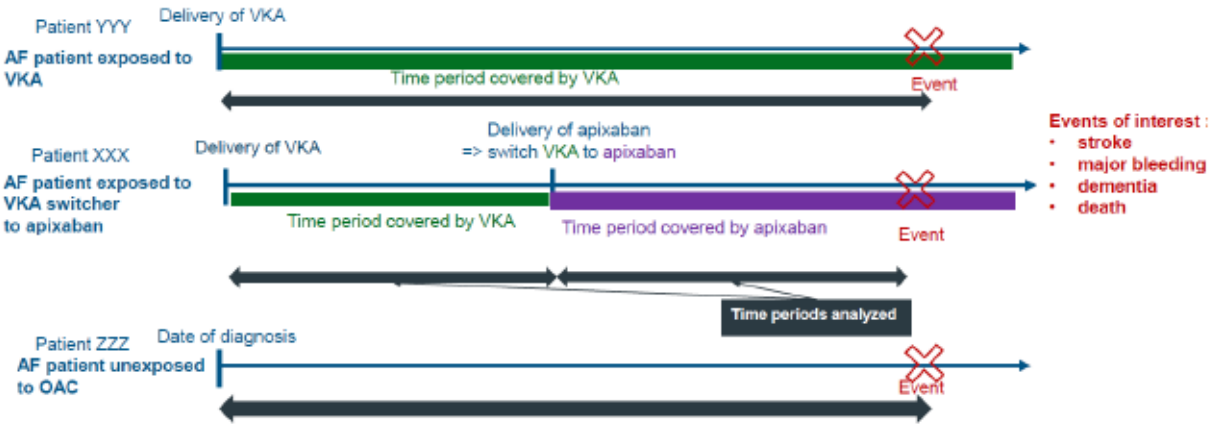
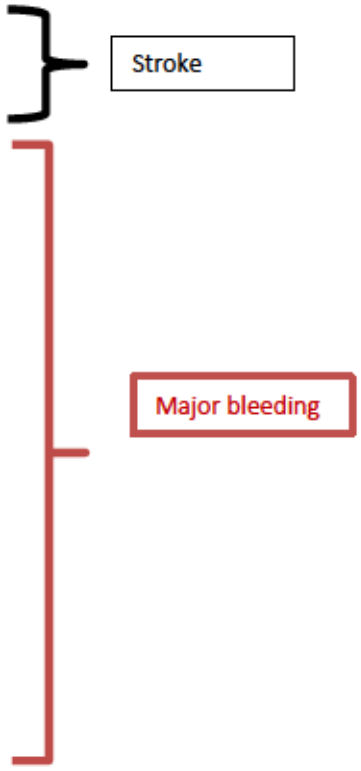


Figure 2 Time periods analyzed in the comparative analysis of events of interest in patients exposed and not exposed to OAC

Appendix 3 Identification of events of interests: stroke and major bleeding

Title	ICD-10 code
Unspecified, ischemic stroke (including Transient ischemic cerebral (TIC))	, I63, I64, G46, G81, G45
Hemorrhagic stroke (including intracranial bleeding)	**I60, I61, I62.9,** S064, S065, S066
Gastric, duodenal and rectal bleeding	I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922
Acute posthemorrhagic anemia	D62
Intraocular bleeding	H356, H431 H450
Otorragia	H922
Hemopericardium	I312
Respiratory bleeding	J942, R04
Haemoperitoneum	K661
Intra articular bleeding	M250
Uterine and vaginal bleeding	N02, N938, N939, N950, R31
Other bleeding	R58, T792



Appendix 4 Identification of medical history and comorbidities

Disease	ICD-10 codes
Coronary arterial disease (CAD)	I21, I22, I24, I25
Sleep disorders	G47
Cancer	C00 to C80, D00 to D09, D37 to D48, Z510, Z511
Malnutrition	E43, E44, E46,
Morbid obesity (BMI>30)	E66
Hospitalisation for anemia	D50, D53
COPD	J44.9
Peripheral arterial disease	I70.0, I70.2, I70.9
Diabetes	E08, E10, E11, E13, E14
Congestive Heart failure	I50.2, I50.3, I50.4

Appendix 5 Identification of treatments and left atrial appendage (LAA) occlusion

Drug- treatments	ATC or CCAM code
Antivitamin K	B01AA
apixaban	B01AF02
rivaroxaban	B01AF01
dabigatran	B01AE07
Selective serotonin reuptake inhibitor antidepressants (SSRIs)	N06AB
Antiarythmics	C01BA, C01BB, C01BC, C01BD, C01BG
Non-steroidal anti-inflammatory drugs (NSAIDs)	M01A;
CYP 3A4 cyt P450 inhibitors	B01AC24, C05AE03, C09BB10, C01BD01, J01FA excepté J01FA02
Proton pump inhibitors	A02BC
Systemic azole antifungals	J02AB et J02AC
Anti-platelet agents	B01AC
Medical procedure of cardioversion	DERP004, DERP003
Other anticoagulants	B01AB, B01AE, B01AF, B01AX
Antihypertensives	ATC: C02, C03, C07, C08, C09 (excluding : C02KX01 (not available in France), C03BA08 (not available for outpatient), C03CA01, C07AA07, C07AA12 (not available in France), C07AG02
glucose-lowering drugs	A10BA Metformin, A10BH DPP-IV inhibitors, A10BJ GLP-1 receptor agonists, A10BX Glinide, A10BF Alpha Glucosidase inhibitors, A10BB Sulfonylurea and the combinations A10BD07, 08, 10 DPP-IV + Metformin and A10BD02 Sulfonylurea + Metformin and A10A insulins
lipid-lowering drugs	Statins: C10AA, C10BA, C10BX; fibrates: C10AB; omega 3 C10AX06; Monoclonal anti-PCSK-9C10AX13 and C10AX14
Beta-blockers	C07A, C07B, C07C, C07D, C07E, C07F
Antivirals, protease inhibitors	J05AE
CCAM code	**LAA occlusion**
DASF074	Non-English text

Appendix 6 Details on HCRU analysis

Description of HCRU and cost to be described in the analysis

This list of HCRU will be described and associated cost will be calculated.

List of HCRU and cost categories that will be extracted

Hospital stay(s) (private and public), including:
- Hospital admission
- Hospital at home
- Rehabilitation and recuperative care facilities
- Palliative care
- Emergency visit

Non-hospital / ambulatory care:
- Outpatient physician's visits (private practice, home or outpatient)
- Outpatient paramedic visits
- Dispensing of observable drugs (AF drugs and other)

Number and frequency of sickness benefits

Number and frequency of reimbursed transports

HCRU and Costs related to AF
- Hospital care with a diagnosis of AF
- Treatment related to AF
- Lab tests
- Medical procedures
- Medical devices (LPP)
- Transportation following an AF hospitalization
- Sick leave and invalidity up to 7 days after AF hospitalization

Appendix 7

Non-English text

Non-English text

Non-English text

Non-English text

Non-English text